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a propagating wave of depolarization to adjacent myocytes. These insights can be used to better understand the basic mechanisms of calcium-entrained cardiac arrhythmias.

3025-Pos Board B130
Self-Organization of Pacemaking Sites for Calcium Waves and Oscillations in Cardiac Myocytes
Michael Nivala, Chris Ko, Alan Garfinkel, James N. Weiss, Zhilin Qu.
Calcium (Ca) sparks are elementary events of intracellular Ca signaling, which tend to occur randomly. Ca waves and whole-cell Ca oscillations occur under Ca overload and disease conditions. How Ca waves emerge from Ca sparks is not completely understood. We developed a three-dimensional model for Ca cycling which contains 100x20x10=20,000 identical Ca release units (CRUs), simulating the CRU network corresponding to a complete cardiac myocyte with dimensions of 100x20x10 micrometers. Using this model, we can generate the well known Ca signaling hierarchy: Ca quarks, Ca sparks, macro-sparks, abortive waves, and full Ca waves. We can also induce spiral waves within the cell, a wave phenomenon widely observed in myocyte experiments. Besides the well known experimental observation that increasing Ca loading promotes these wave dynamics, we also make the following observations: 1) The diffusion rate of Ca is a key parameter. Spontaneous Ca waves occur only when the diffusion rate is above a critical value. 2) When the model is homogeneous, Ca waves originate from different locations via a self-organizing process. This self-organizing process is influenced by, but does not require, heterogeneity. 3) When the model contains heterogeneities, such as heterogeneous Ca release channel distribution, Ca waves can originate from different locations or occur repeatedly from the same location. In real cardiac rabbit ventricular myocytes loaded with Fluo-4 AM to image intracellular Ca, Ca waves typically originate from different locations after successive rapid pacing episodes. In conclusion, our results indicate that Ca waves in cardiac myocytes originate predominantly as a result of self-organizing processes rather than pre-existing heterogeneities.

3026-Pos Board B131
Ca^{2+} Leak and Ca^{2+} Sparks in Mammalian Heart: Insights from a Computational Model
George S.B. Williams, Aristide C. Chikando, W. Jonathan Lederer, Eric A. Sobie, Hoang-Trong M. Tuan, M Saleet Jafri.
Calcium (Ca2+) signaling in muscle, neuronal, and non-excitable cells has benefited significantly from advances in biological tools and imaging technology, however, the molecular interactions of nanoscopic molecules, structures and compartments has been challenging to study under physiological conditions. Here, we exploit novel computational modeling techniques to examine real-time molecular and cellular physiology in cardiac ventricular myocytes. The model focuses on local and cell-wide Ca2+ signaling phenomena related to calcium induced calcium release from intracellular calcium channels, ryanodine receptors (RyR2s), located on the sarcoplasmic reticulum (SR) membrane. This work is informed by the latest molecular investigations and recent characterizations of channels, transporters, and buffers located in mammalian heart. We have created a detailed, whole-cell model of Ca2+ signaling using a realistic number of calcium release units (CRU) each containing a cluster of stochastically gating RyR2s. During systole the opening of these RyR2s is triggered by Ca2+ entry via voltage gated L-type Ca2+ channels. The synchronized opening of the RyR2 cluster leads to localized elevations of [Ca2+]i known as Ca2+ sparks. During diastole Ca2+ sparks are still observed and are attributed to the finite opening rate of the RyR2. RyR2s are also believed to display unsynchronized or non-spark openings where only a few channels in the CRU open without triggering the remainder of the RyR2 cluster. This non-spark Ca2+ release would be below current experimental detection thresholds and therefore ‘‘invisible.’’ These spark and non-spark openings of RyR2s constitute a molecular basis for Ca2+ leak from the SR. The computational model suggests that a significant fraction of SR Ca2+ leak is due to RyR2s openings that fail to trigger a ‘‘visible’’ Ca2+ spark. Additionally, the fraction of non-spark or ‘‘invisible’’ SR Ca2+ leak increases as SR Ca2+ content declines.

3027-Pos Board B132
GPU-Enabled stochastic Spatiotemporal Model of Rat Ventricular Myocyte Calcium Dynamics
Tuan M. Hoang-Trong, George S.B. Williams, Jonathan W. Lederer, Saleet Jafri.
The dysfunction of the normal calcium dynamics is a major factor in certain types of cardiac arrhythmias. These cardiac arrhythmias are thought to result from Ca^{2+} waves which occur when Ca^{2+} release propagates from one release site to another outside of the normal time during systole resulting in depolarization of the cell's outer membrane. Experimental results suggest that the elementary event underlying calcium release at these sites is the Ca^{2+} spark and the summation of these Ca^{2+} sparks result in the global $[Ca^{2+}]_i$ transient that causes contraction. We have developed a model of the cardiac myocyte that includes the spatial organization and microsecond level resolution of clusters of ryanodine receptor (RyR) that are Ca^{2+} release channels responsible for the generation of Ca^{2+} sparks. We use this model to explore how Ca^{2+} overload, RyR Ca^{2+} sensitivity, RyR coupling, and other factors that affect the propagation of Ca^{2+} release between release sites. We will utilize our newly developed Ultrafast Markov chain Monte Carlo method which allows the rapid simulation of a whole-cell model containing 20,000 release sites, each containing 7 L-type Ca^{2+} channels and 50 RyRs. This algorithm greatly reduces computation time by using adaptive time step approach and a compact representation of the Markov chain state space. Hence, this novel method provides a powerful tool for performing stochastic cellular simulation with realistic Ca^{2+} dynamics. Also, with the availability of the next generation graphics processing units (GPU) computing architecture - codename Fermi from NVIDIA - model solution is greatly accelerated allowing the implementation of such a detailed model for the first time.

3028-Pos Board B133
Contributions of Structural t-Tubule Heterogeneities and Membrane Ca^{2+} Flux Localization to Local Ca^{2+} Signaling in Rabbit Ventricular Myocytes
Peter M. Kekenes-Huskey, Yuhui Cheng, Johan Hake, Frank Sachse, John Bridge, J.A. McCammon, Anushka Michailova.
The micro-architecture of the transverse tubular system (t-system) and the arrangement of associated proteins are central to the function of ventricular cardiomyocytes. Recently, confocal imaging and image processing was used to characterize the geometry of the t-system in rabbit ventricular cells [1]. The average diameter of single t-tubules was estimated to be 448+-172 nm with constrictions occurring every 1.87+-1.09 um along their principal axis. Here, we used mathematical modeling to investigate how local variations in t-tubular cross-sectional area and the distribution of membrane Ca^{2+}flux regulate Ca^{2+}-entry, diffusion and buffering in rabbits [2]. The current model includes a realistic geometry of a single t-tubule, its surrounding half-sarcomeres, the spatially distributed Ca^{2+}transporting proteins along the cell membrane (L-type Ca^{2+} channel, Na^{+}/Ca^{2+} exchanger, sarcolemmal Ca^{2+} pump) as well as stationary and mobile Ca^{2+} buffers (troponin C, ATP, calmodulin, Fluo-3). A finite element software package CSMOL was used to solve the coupled reaction-diffusion PDE system describing the time-dependent concentration profiles of the above-listed species.[3]. The model was parameterized according to voltage-clamp data in rabbit ventricular myocytes with Ca^{2+} release at the sarcoplasmic reticulum disabled pharmacologically [4]. The results indicate that the constrictions and spatial arrangements of membrane Ca^{2+} proteins may cause local inhomogeneities in Ca^{2+} concentration. In addition, we examined the activation of a catalytic Ca^{2+}-binding site on Na^{+}/Ca^{2+} exchanger on local Ca^{2+} gradients in the presence or absence of fluorescent dye.
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[2]Cheng*et al.*, *PLoS CompBiol* 2010, (in press).
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[4]Sobie et al., *Biophys J: Biophys Lett*:L54-L56,2008.
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3029-Pos Board B134
How Does RyR2-Mediated SR Calcium Leak Fail to Cause Sparks?
Daisuke Sato, Donald M. Bers.
Recent experiments have shown that Ca leak from the sarcoplasmic reticulum (SR) can occur via spontaneous Ca sparks, non spark ryanodine receptor (RyR) mediated leak, and RyR independent pathways (Zima *et al.BJ,* 94:104a, 2008). Opening of a single RyR is expected to increase local [Ca] in the cleft space rapidly (<< 1 ms) to levels that are expected to activate neighboring RyR in that cleft via Ca induced Ca release. Our question is how and why RyR-mediated SR Ca leak becomes mainly non-spark mediated at moderate to low SR Ca loads. To answer this question, we analyze Ca flux through RyRs using a physiologically detailed mathematical model of junctional SR Ca release in which RyR gating is regulated by intra SR and cleft [Ca] ($[Ca]_{SR}$ & $[Ca]_{Cleft}$). In this model, there are one hundred RyR channels in one Ca release unit. Each RyR opens stochastically depending on $[Ca]_{Cleft}$ and $[Ca]_{SR}$. We